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| APPLICATION NO | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO | CONFIRMATION NO |
|-----------------------------------------------------------------------------------------------------|-------------|----------------------|---------------------------|-----------------|
| 09 490,208 | 01 24 2000 | C. Frank Bennett | RTS-0066 | 6872 |
| 7590 | 05 06 2003 | | | |
| Jane Massey licata Law Offices of Jane Massey Licata 66 East Main Street Marlton, NJ 08053 | | | EXAMINER MCGARRY, SEAN | |
| | | | ART UNIT 1635 | PAPER NUMBER |

DATE MAILED: 05/06/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|------------------------|---------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/490,208 | BENNETT ET AL. |
| | Examiner | Art Unit |
| | Sean R McGarry | 1635 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 16 October 2000 and 12 February 2003.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1,2 and 4-14 is/are pending in the application.
 - 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) Claim(s) ____ is/are allowed.
- 6) Claim(s) ____ is/are rejected.
- 7) Claim(s) ____ is/are objected to.
- 8) Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on ____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on ____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 - 1 Certified copies of the priority documents have been received.
 - 2 Certified copies of the priority documents have been received in Application No. ____.
 - 3 Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 - a) The translation of the foreign language provisional application has been received.

Attachments

- 1) Notice of Allowance or Restrictioner (if applicable)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____

- 4) Interview Summary (if applicable)
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____

Art Unit: 1635

DETAILED ACTION

1. Applicant's election with traverse of antisense targeted to SEQ ID NO: 3 and the cancellation of claim 3 drawn to the specific antisense oligonucleotides subject to restriction is acknowledged and noted. The restriction requirement directed to a specific oligonucleotide is moot in view of the cancelation of claim 3. Applicant argues the restriction requirement drawn to the target sequences with the arguement that the search would not be a burden and that MPEP 803.04 has determined that 10 sequences is normally a reasonable number for examination. It is the position of the examiner that a burden would exist for the search and examination of all the sequences since, for example since a separate search would be required for each sequence. Each search produces a different result set and the different sets all need to be search for prior art , for example. MPEP 803.04 allows for up to 10 sequences to be searched. Due to the complex nature of the art and due to the large size of the nucleic acid databases and the burden such searches place on the office search system one (1) sequence has been determined to be a reasonable number for search and examination.

The requirement is still deemed proper and is therefore made FINAL.

2. Applicant's arguments with respect to claims 1-14 have been considered but are moot in view of the new ground(s) of rejection

Art Unit: 1635

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1, 2 and 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ding et al, Peresleni et al, and Leesoon-Wood et al in view of Nunokawa et al [US 6,203,982] and Monia et al. [US Patent No. 5,872,242].

Ding et al disclose a 21mer phosphorothioate antisense oligonucleotide targeted to bases 1-21 of the murine iNOS mRNA and disclose the administration of said oligonucleotide to SJL/J mice as an animal model for multiple sclerosis via injection with a sterile saline solution.

Art Unit: 1635

Peresleni et al disclose a phosphorothioate antisense oligomer targeted to the 5' UTR/initiation codon/ region of human iNOS mRNA and disclose the inhibition of human iNOS in BSC-1 kidney tubular epithelial cells (see abstract and page 972, for example).

Leesoon-Wood et al disclose the inhibition of C3H 10T1/2 cells via the administration of 15mer antisense oligonucleotides targeted to iNOS mRNA.

Further, the above these references teach the implications of iNOS in pathological conditions and the benefits of inhibiting the expression of iNOS to determine the possible role of iNOS in such pathological conditions.

None of these references specifically disclose antisense oligonucleotides comprising modified sugar moieties or modified nucleobases, chimeric antisense oligonucleotides or a colloidal dispersion system or teach targeting SEQ ID NO: 3.

Nunokawa et al have also taught conditions associated with iNOS and the benefit for inhibiting iNOS expression. Nunokawa et al have provided a method for screening compounds that inhibit iNOS and further have taught SEQ ID NO: 3 as a an iNOS nucleic acid for inhibition.

Monia et al have taught antisense oligonucleotides comprising modified sugar moieties, antisense oligonucleotides comprising modified nucleobases, chimeric antisense oligonucleotides and modes of delivery such as cholesterol or other lipid moieties. At columns 6-9 these limitations have been taught in general and specifically where the benefits of these modifications in antisense techniques has been taught

Art Unit: 1635

Since Ding et al, Peresleni et al, Leesoon-Wood et al and Nunokawa et al have taught the implications of iNOS in pathological conditions and the benefits of inhibiting the expression of iNOS to determine the possible role of iNOS in such pathological conditions via antisense techniques and Monia et al have taught the specific modifications and there benefits in antisense techniques it would have been obvious to combine the teachings of these references to make the instant invention.

The invention as a whole would therefore have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final

Art Unit: 1635

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean McGarry whose telephone number is (703) 305-7028 (M-Th 6:00-4:30).

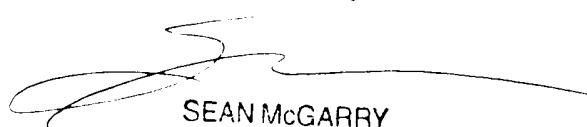
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. Papers should be faxed to Art Unit 1635 via the PTO Technology Center Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see C.F.R. 1.6(d)). The Art Unit 1635 FAX number is (703) 308-4242 or (703) 305-3014. NOTE: If Applicant **does** submit a paper by Fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Sean McGarry

May 5, 2003



SEAN McGARRY
PRIMARY EXAMINER

Technology Center 1600